REMARKS

Prior to entry of this Amendment, Claims 1-10 and 12-18 were pending in the application. In this Amendment, Claims 1, 5, 9 and 15 are amended, and Claims 2, 4 and 10 are cancelled. Claim 17 is withdrawn as being drawn to a non-elected species. Claim 19 is new and has support throughout the specification, for example on page 6, lines 3-4. Upon entry of the Amendment, Claims 1, 3, 5-9 and 12-19 are pending in the application. The Examiner is respectfully requested to reconsider and withdraw the rejection(s) in view of the amendments and remarks contained herein.

REJECTION UNDER 35 U.S.C. § 112

Claims 1-5, 9, 10, 12, 14-16, and 18 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claims are alleged to contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

The Office Action alleges that Claims 1 and 15 introduce new matter, specifically objecting to the phrase, "wherein said medium is capable of inducing regeneration of at least cell type which provides a therapeutic effect in or near a tissue defect." (Action at page 3). Without acquiescing to this allegation, Applicant has amended Claims 1 and 15 to recite, "wherein said medium is capable of repairing or enhancing the bone or cartilage tissue defect." Support for this amendment can be found in the specification as originally filed, for example on page 4, paragraph [0010] and on page 5, paragraph [0011]. Applicant respectfully requests that the

present rejection under 35 U.S.C § 112 first paragraph of Claims 1-5, 9, 10, 12, 14-16, and 18 be reconsidered and withdrawn.

Claims 1-5, 9-12, 14-16 and 18 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claims are alleged to contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with it is most nearly connected, to make and/or use the invention.

The Office Action alleges that the claims "are very broad in that they encompass methods and compositions for treating any tissue defect in a human or other animal subject." Furthermore, the rejection states that one of ordinary skill in the art "would need to perform a large quantity of experimentation to identify all tissue cultures exposed to an electromagnetic field which result in media which are effective in treating all tissue defects, of which there are many types with complex and different characteristics."

Applicant respectfully submits that the amendments to Claims 1 and 15 overcome the enablement rejection. The claims no longer recite treating "any tissue defect." Rather, the claims have been amended to recite treating bone or cartilage defects. Support for the present amendments can be found in the specification as originally filed at page 4, paragraph [0010] and Examples 1 and 2 on pages 9 and 10. Moreover, Applicant has amended the claims to refer only to culturing endothelial cells, which obviates and renders moot the allegation that the claims would require undue testing "to identify all tissue cultures exposed to an electromagnetic field."

Applicant has throughout the specification explained in detail how to perform and use the claimed methods for treating the bone and cartilage defects. The level of skill possessed by one of ordinary skill in the present field of tissue repair is high (PhD or MD). One of ordinary skill, with guidance provided by the Applicant's specification and knowledge freely available at the time of

filing, would have known how to make the claimed compositions and how to use them in subjects having bone or cartilage tissue defects. Applicant respectfully requests that the rejection under 35 U.S.C § 112 first paragraph enablement Claims 1-5, 9-12, 14-16 and 18 be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 102

Claims 9, 11, and 14 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,195,940, Baylink, issued March 23, 1993 (herein "*Baylink*"). This rejection is respectfully traversed.

Baylink discloses a specific objective to provide non-invasive techniques for stimulating the production of growth factors in the tissue of interest. (*Baylink* at Col. 1, lines 7-13.) The production of the growth factor occurs *in vivo*. (*Baylink* at Col. 2, lines 5-8). *Baylink* thus fails to disclose either a composition comprising a safe and effective amount of a tissue culture medium produced by pulsed electromagnetic stimulation of an endothelial cell tissue culture for at least about 8 hours, or a pharmaceutically-acceptable carrier. Since *Baylink* fails to disclose each and every claim element recited in the presently amended Claim 9, it is respectfully submitted that a *prima facie* case of anticipation cannot be met. Since Claim 11 was previously cancelled and Claim 14 depends directly from Claim 9, the rejection with respect to these claims is rendered moot. Applicant respectfully requests that the present rejection under 35 U.S.C § 102(b) of Claims 9, 11 and 14 be reconsidered and withdrawn.

Claims 9, 11, and 14 are rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,334,069, George et al., issued December 25, 2001, (herein "*George*"). This rejection is respectfully traversed.

Applicant respectfully submits that *George* also fails to anticipate the amended Claim 9 and thus claims dependent thereon, for the same reasons stated above for *Baylink*. For example, *George* fails to teach or suggest the use of a composition comprising tissue culture medium produced by pulsed electromagnetic stimulation of an endothelial cell. As such, it is respectfully submitted that a *prima facie* case of anticipation cannot be met. Since Claim 11 was previously cancelled and Claim 14 depends directly from Claim 9, the rejection with respect to these claims is rendered moot. Applicant respectfully requests that the present rejection under 35 U.S.C § 102(b) of Claims 9, 11 and 14 be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 103

Claims 1-5, 9, 10, 12, 14-16, and 18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,372,494, Naughton, issued April 16, 2002 (herein "*Naughton*"), in view of *Baylink* and/or *George* and further in view of Guerkov et al., Pulsed Electromagnetic Fields Increase Growth Factor Release by Nonunion Cells, *Clinical Orthopaedics and Related Research*. 2001. 384: 265-279 (herein "*Guerkov*"). This rejection is respectfully traversed.

Naughton is drawn to compositions comprising conditioned media and three dimensional tissue constructs for various therapeutic purposes, including wound healing, and to repair and correct a variety of anomalies, both congenital and acquired, as well as cosmetic defects, both superficial and invasive. (*Naughton* at Col. 25, lines 39-41). *Naughton* further teaches a conditioned media that contains various growth factors and other therapeutic products produced by human cells that have been cultured for a period of time to produce a desired level of extracellular products. *Naughton* preferentially describes three-dimensional cell constructs

versus two-dimensional cell constructs, stating "The cell type, whether cultures in two-dimensions or three-dimensions, will affect the properties of the conditioned medium. A three-dimensional construct is preferred." (*Naughton* at Col. 10, lines 12-15). *Baylink* and *George* have been discussed above.

Baylink and *George* teach the application of an electromagnetic field *in vitro* to human osteosarcoma cancer cells and fibroblasts respectively. *Baylink* teaches increased production of growth factor by osteosarcoma cancer cells when treated with a magnetic field. *George* on the other hand, merely teaches that the fibroblasts used in the experiment proliferate in the presence of a pulsed electromagnetic field when compared to non-treated fibroblasts. Neither reference teaches nor reasonably suggests that endothelial cells are capable of producing a tissue culture medium that can be used to repair or enhance bone, cartilage or wound tissue defects.

Guerkov describes a study developed to determine whether there is a response by non-union cells to produce growth factors, in particular TGF-β1 after being treated with pulsed electromagnetic fields (PEMF). *Guerkov* treats non-union cell cultures using PEMF consisting of 4.5 ms bursts of 20 pulses repeating at 15 Hz. (*Guerkov* at page 269, col. 2.). The two populations of nonunion cells studied were derived from seven patients with hypertrophic and atrophic nonunions. (*Guerkov* at page 267, col. 2) These cells were probably fibroblastic (*Guerkov* at page 276, col. 1) and not chondrocytes or osteoblasts. *Guerkov* states, at page 277, col. 1, lines 29-48, "The levels of TGF-β1 produced in response to pulsed electromagnetic field stimulation were sufficient to elicit a response if committed chondrocytes or osteoblasts had been present and if the growth factor was in active form." Production of growth factor TGF-β1 was dependent on the type of nonunion tissue from which the cells were isolated. Hence one of ordinary skill in the art would not conclude that PEMF works on every cell culture type or that

any one type of growth factor can be induced from any cell culture type using PEMF in vitro. Of particular note, with respect to cell proliferation, PEMF stimulation "**had no significant effect at any of the times examined**." (See Figure 4A with respect to cell proliferation at page 272, col.2). Hence, in regards to nonunion cells (fibroblasts) from bone defects, PEMF had no effect on cell proliferation and teaches away from *Baylink* and *George* as an effective means to stimulate cell proliferation or growth. In conclusion, *Guerkov* states on page 276, col. 2, lines 10-14, that **PEMF "did not affect cell proliferation, differentiation, or matrix synthesis during the study."**

Applicant respectfully submits that there is no nexus between the teachings of *Naughton*, *Baylink*, *George* and *Guerkov* and the use of PEMF on endothelial cells to obtain a tissue culture medium for repairing and enhancing bone, cartilage and wound defects. In fact, *Guerkov* teaches away from the use of PEMF to increase the number of cells that are present in nonunion bone defects. Hence one of ordinary skill in the art would not combine the teachings of *Naughton* further in view of *Baylink* and *George* with *Guerkov* to arrive at Applicant's invention.

Since the combination of the references of record fail to disclose each and every claim limitation of the presently amended claims, a *prima facie* case of obviousness has not been met. Accordingly, Applicant respectfully requests that the present rejection under 35 U.S.C § 103(a) of Claims 1-5, 9, 10, 12, 14-16, and 18 be reconsidered and withdrawn.

Claims 1, 3, 9, 12, 14, and 15 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over PCT International Application Publication WO 93/04164, Shipley, published March 4, 1993 (herein "*Shipley*") in view of *Baylink* and/or *George* and further in view of *Guerkov*. This rejection is respectfully traversed.

Shipley is directed to the production of growth factors by human epithelial cells

(keratinocyte-derived conditioned medium factors) (kdCMF) in protein free medium and conventional tissue culture techniques and using the same to increase the rate of wound healing. The Office Action assumes that such methods for culturing cells *in vitro* to produce growth factors are completely interchangeable with methods to produce the same growth factors by cultured cells using PEMF. This assumption is neither supported in the references of record, nor is there a reasonable expectation that such interoperability exists.

The Office Action alleges that PEMF could be used to treat tissue cultures during incubation and prior to the extraction of the conditioned medium when performing the *Shipley* invention. The Office Action alleges that one of ordinary skill in the art would have been motivated to do this since the application of an electromagnetic field would have increased growth factor production, thus resulting in a conditioned medium with higher concentration of growth factors. However, *Guerkov* teaches that nonunion bone cells are incapable of proliferation after PEMF treatment when compared to non-PEMF treated cells despite an increase in the level of growth factor produced in these PEMF treated cells. One of ordinary skill in the art would have viewed *Guerkov* to teach that, despite the increased production of a growth factor, certain cell types may not proliferate, differentiate, or alter matrix synthesis in the presence of PEMF. Furthermore, there is no reasonable expectation of success that would lead one of ordinary skill in the art to conclude that the epithelial cells of *Shipley* could be induced to produce a tissue culture medium that could repair or enhance bone, cartilage or wound tissue defects using PEMF, because the cells in *Shipley* are completely different from the cells in *Baylink* and/or *George*.

Applicant respectfully submits that a *prima facie* case of obviousness based on the references *Shipley* in view of *Baylink* and/or *George* and further in view of *Guerkov* has not been

made. Accordingly, Applicant respectfully requests that the present rejection under 35 U.S.C § 103(a) of Claims 1, 3, 9, 12, 14, and 15 be reconsidered and withdrawn.

CONCLUSION

Applicant respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 241-1600.

Respectfully submitted,

Dated: April 1, 2009

By: _____

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